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Research Article

3D printed Tablets for Personalized Medicine

Formulation and Evaluation of 3D Printed Pregabalin Tablets Targeted For Neuropathic Pain By Qbd Approach For Personalized Medicine

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Abstract: The 3D printing technology has been newly employed in the design and formulation of different dosage forms with the aim of formulation and evaluation of 3D printed Pregabalin tablets for the treatment of neuropathic pain by QbD approach. Drug (Pregabalin) together with other excipients, were mixed and extruded into filaments by hot melt extrusion. Then with the help of fused deposition modeling these obtained filaments were printed into tablets. Due to the use of different polymers in the printed formulation, different release profiles for the 3D printed tablets were obtained. Drug release characteristics, change the infill or the size of the printed tablets, allowing the personalization of the tablets. Filaments and tablets were characterized by means of Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), X- RAY powder diffraction (XRPD), and thermo gravimetric analysis (TGA). The results showed that after printing, the processing condition did not have a significant impact on the stability of the drug and the crystalline nature of the drug remained. Fused deposition modeling (FDM) 3D printing makes it possible not only to formulate 3D printing Pregabalin tablets for the treatment of neuropathic pain but also to modify the potential of additive manufacturing in the development of personalized dose medicines. This study presents novel formulations containing Pregabalin for prevention of neuropathic pain and investigates 3D printing technology for personalized production of oral solid dosage from enabling adjustable dose as well as drug release properties.

Keywords: 3d Printing Tables, Pregabalin, Hot Melt Extrusion, Fused Deposition Modeling, And Personalized Medicine.

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1. INTRODUCTION

Neuropathic pain can be defined as a process occurring after a primary lesion or disease of the somatosensory nervous system. [1]This condition is the result of a series of different pathological mechanisms and it is usually described based on the anatomic localization or etiology.[2] The condition and the pathophysiological state that determine the onset of neuropathic pain mostly involved are metabolic disorder (e.g. peripheral diabetic neuropathy(PDN)), neuropathies associated with viral infections (e.g. post-herpetic neuralgia, HIV, leprosy), autoimmune disorder affecting the central nervous system (e.g. multiple sclerosis and Guillain-barre syndromes), chemotherapy- induced peripheral neuropathies, damage to the nervous system of traumatic origin (e.g. spinal cord injury (SCI) and amputation) and inflammation. Neuropathic pain is usually chronic, difficult to treat, and often resistant to standard analgesic management and this pain is initiated or caused by a primary lesion or dysfunction in the nervous system.[3] Pregabalin is a new synthetic molecule with favorable pharmacokinetic profile compared with gabapentin.[4]Anticonvulsant medications are established treatments for neuropathic pain.[5] Neuropathic pain is the chronic pain resulting from injury to the nervous system. The injury can be to the central nervous system or the peripheral nervous system. Neuropathic pain can occur after trauma and many disorders exists such as multiple sclerosis and stroke.[6] This type of pain is notoriously difficult to treat. Pregabalin is a lipophilic GABA (gamma amino butyric acid) analog substituted at the 3' position; this facilitates diffusion across the blood- brain barrier.[7] Efficacy of Pregabalin has been proven in neuropathic pain.[8] 3D printing is an emerging technology that can be well suited to manufacturing of personalized medicine.[9,10] Personalized 3D printing drug products could particularly benefit patients who are known to have a pharmacogenetic polymorphism or who use medication with narrow therapeutic indices. Health care providers can analyze the pharmacogenetic profile as well as other demographic information of a patient for specific dose which could be developed based on clinical response to treatment.[11] 3D printing focuses mainly for patient based specifications. In addition, 3D printing has the potential of producing a dosage form of several active ingredients, either as a single matrix or as complex multi-compartment 3D printed tablets.[12] In addition, complex formulations such as connected dosage forms with mixed release kinetics and complex designs have been carried out to manage better patient compliance and better therapeutic outcomes. FDM, a technology developed in the late 1980s, is also one of the most widely studied technologies in pharmaceutics. Pregabalin, a chemical analogue of neurotransmitter gamma amino butyric acid (GABA), is a receptor agonist which has analgesic, anticonvulsant and anxiolytic activities. [13,14] Immediate release formulations of Pregabalin, available in different dosage strength are approved by the FDA for the management of diabetic peripheral neuropathy, fibromyalgia, post-herpetic neuralgia, and also as adjunctive therapy for partial seizures.[15] However, Pregabalin has a short elimination half-life of approximately 6 h.[16] According to the Biopharmaceutics classification system (BCS), Pregabalin is a class I compound with high solubility and high permeability. Moreover, the drug has been proven to be mainly absorbed in the stomach and upper gastrointestinal tract. Previously, an intragastric floating tablet of domperidone was formulated using 3D technology. As FDM, 3D technology requires filaments as the main material, where hydroxy-propyl cellulose filaments loaded with domperidone were prepared using hot melt extruder and hollow tablets were made using a 3D printer. Printed tablets were studied for invitro and in vivo floating time and drug release profile, which demonstrated a promising application of FDM technology to reduce the frequency of administration and improve patient compliance.[17] Our study, was aimed to formulate and evaluate 3D printed Pregabalin tablets for the treatment of neuropathic pain by QbD approach.

2. MATERIALS AND METHODS

2.1 Materials

Pregabalin was purchased from Lupin laboratories, Goa. HPMC E15 LV, Hydroxy-propyl methyl cellulose, polyvinyl alcohol (PVA), polyethylene glycol (PEG 400), Ethyl cellulose (EC), starch, and croscarmellose sodium was purchased from Lobachemie Pvt. Ltd Mumbai (India). All the chemicals and reagents used in this study were of analytical grade.

2.2 Method

2.2.1 Fused Deposition Modeling

Fused deposition modeling (FDM) is an additive manufacturing process that belongs to the material extrusion family. In FDM, an object is built by selectively depositing melted material in a predetermined path layer-by-layer. The materials used are thermoplastic polymers and come in a filament form.[18] FDM is the most widely used 3D Printing technology .It represents the largest installed base of 3D printers globally and is often the first technology people are exposed to. [19]In this article, the basic principles and the key aspects of the technology are presented. UV-visible spectrophotometer (Shimadzu UV-1800, Japan) FTIR Spectrophotometer (Perrkin Elmer spectrum 2, UK), 3D printer (Flash forge, Inventor) dissolution apparatus type II, (model.No.40)

2.2.2 Preparation of drug loaded filament (Step wise)

10 gm of blend of drug and excipients was prepared

⇩

The excipients were mixed with mortar and pestle with the drug until a number of drug particles and polymer were observed.

⇩

The theoretical drug content of the mixture was 5 TO 50 W/W.

⇩

The mixture of drug and excipients was then extruded using a single screw filament (Extrusion temperature 120 to 125 ^{0}C nozzle diameter of 1.5mm, rotational speed of 10 to 20 rpm).

⇩

Tablet print speed including infill print speed and outer perimeter print speed were all maintained at 30 mm/s.

Table No. 1- Formulation table of 3D printing Pregabalin tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Pregabalin	100	100	100	100	100	100
Hydroxy-propyl Methylcellulose ($HPMCE_{15}LV$)	20	35	25	-	45	45
Polyvinyl alcohol (PVA)	25	10	20	45	-	-
Polyethylene glycol (PEG) 400	2	2	2	2	2	2
Starch	1	1	1	1	3	1
Croscarmellose sodium(CCS)	1	1	1	1	1.5	1
Ethyl cellulose (EC)	1	1	1	1	1	1

Table 1 Shows formulation of 3D printing Pregabalin tablets. Active ingredients for the formulation include: Polyethylene glycol (PEG 400), Pregabalin. The amount of the active ingredients and excipients required in each drug formulation (F1, F2,F3, F4, F5, and F6) is shown in the table 1.Tablets were designed using flash frog 3D printer flashpoint software version 1.1.4. (Autodesk, Rafael, USA).Pregabalin is same in every formulation (100 mg). Formulation 4 (F4) does not have $HPMCE_{15}LV$ and Formulation 5 and 6 (F5, F6) do not have PVA.

2.2.3 Design and printing of tablets

Tablets were designed using flash frog 3D printer flashpoint software version 1.1.4. (Autodesk, Rafael, USA) cylindrical tablets were designed for preliminary studies and novel shapes of tablets were designed for optimized formulation.

2.3 Characterization of 3D printed Pregabalin tablets

2.3.1 UV- visible spectrophotometer

2.3.1.1 Determination of wavelength for maximum absorption

A concentration 100 µg/ml Pregabalin was dissolved in distilled water scanned over a wavelength range of 200-400 nm.

2.4 Preparation of standard calibration curve of Pregabalin

10mg of Pregabalin accurately weighted by electronic balance and dissolved in 10ml of distilled water in 100ml volumetric flask. Content of flask was kept on Sonicator for well mixing of solution for 10 min and transferred in 10ml volumetric flask. 1000µg/ml solution was prepared. From prepared standard stock solution, 1 ml solution was prepared and from this solution, pipetted out 0.2ml, 0.4ml, 0.6ml, 0.8ml, 1.0ml, 1.2ml of solution and made up to 10ml which leads to 2µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml & 12 µg/ml concentration solution. This solution was estimated for the drug by UV spectrophotometer by using water as blank at 275 nm.[20]

2.5 Compatibility Study

The formulation of the complex can be confirmed by FTIR spectrometry, comparing the spectrum of the complex with the spectrum of the individual components and their physical mixtures. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks, and appearance of new peaks due to excipient interaction. This spectral analysis was employed to check the compatibility of drug with the excipients used.[21]

2.6 Differential scanning calorimetry (DSC)

Pure Pregabalin filament was analyzed using DSC (SETARAM Instrumentation, France, model Themys one plus) apparatus to study the effect of temperature. Sample was heated from 25-250°C with a heating rate of 10°C/min in the atmosphere of nitrogen.[22]

2.7 Scanning electron microscopy (SEM)

The SEM study was performed using scanning electron microscope [Field Electron & Ion Company, USA, model Apreo Lo Vac] to study the morphology of the filaments.[23]

2.8 Design of Experiment

A QbD based approach using a central composite design - a response surface design expert software 9.05 was employed to systematically study the combined influence of the formulation and process variables such as Infill (X1%), Dimension (X2, mm), and print speed (X3 rpm) on critical quality attributes (CQAs) of the product i.e. the disintegration time. A statistical model incorporating interactive and polynomial term was used to evaluate the response employing the equation.[24]

$$Y=b0+b1X1+b2X2+b3X3+b4X12+b5X22+b6X32+b7X1X2+b8X1X3+b9X2X3$$

Where Y is the dependent variable, b0 is the intercept representing arithmetic mean response of the runs, and b1 to b9 is the estimated coefficient for the factor (xi, i=1,2,3) and X3 the coded level of the independent variable. The interaction term (X1X2, X2X3, and X1X3) showed how the response changes when all three factors were simultaneously changed. The values of the central composite design batches are shown in Table no.2 and disintegration time are shown in Table no. 3.

Table No.2 - coded level and real value for each factor under study

Variables	Levels		
	-1 Low	0 Medium	1 High
Infill X1 (%)	25	50	80
Dimension X2 (mm)	5	7.5	10
Print speed X3 (rpm)	5	10	15

Table 2 Showing coded levels and real value for each factor in study. There are three levels i.e. low, medium, and high. Each variable (Infill X1, Dimension X2, and Print speed X3) has a specific value at specific level (low, medium, high). At low level (-1) the infill X1 (%), print speed (X3) and dimension (X2) are lowest i.e. 25%, 5 rpm and 5mm respectively. On the other hand the infill (X1), print speed (X3) and dimension (X2) are highest at high level (1) i.e. 80% ,15rpm and 10mm respectively. The medium level (0) has values of the three variable in between values of high level and low level.

2.9 Invitro dissolution studies

Apparatus: USP apparatus II (paddle)
Agitation speed (rpm): 100rpm
Medium: 6.8pH phosphate buffer
Volume: 900ml
Temperature: 37.0±0.5^{0}C
Time: 2, 4, 6, 8, 12, 24hrs
Wavelength: 268nm

A sample (5ml) of the solution was withdrawn from the dissolution apparatus at specific time intervals, and the sample was replaced with fresh dissolution medium: the sample was filtered through whatman filter paper and from the filtrate 1ml was taken and diluted to 10ml. Absorbance of these solution was measured at 268nm using UV spectrophotometer (Shimadzu (UV-1800), Japan)

3. STATISTICAL ANALYSIS

The statistical analysis was carried out by using the software Graph Pad Prism (San Diego, CA). Mathematical models were used to evaluate the mechanism of drug release from the tablets and kinetics. Based on the correlation coefficient (r) value in various models, the bestfit model was selected.

4. RESULTS

4.1 Determination of λmax

Pregabalin concentration in distilled water was found to be 100 µg/ml at 268nm.

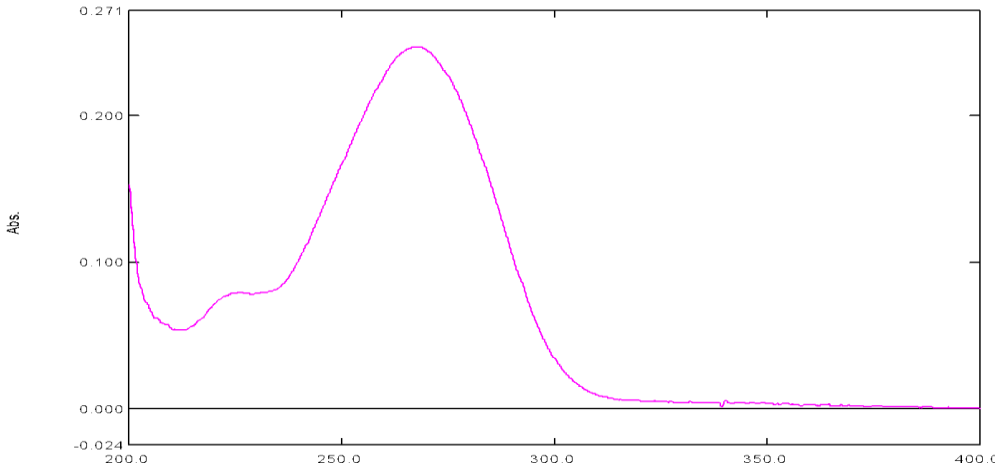

Fig No. 1: UV spectra of Pregabalin

4.2 Preparation of standard calibration curve of Pregabalin

The UV absorbance of the Pregabalin standard solution in the range of 2-12 µg/ml in distilled water showed linearity at λmax 268 nm. The linearity was plotted for absorbance against concentration with R^2 value 0.997 for distilled water (figure 2).

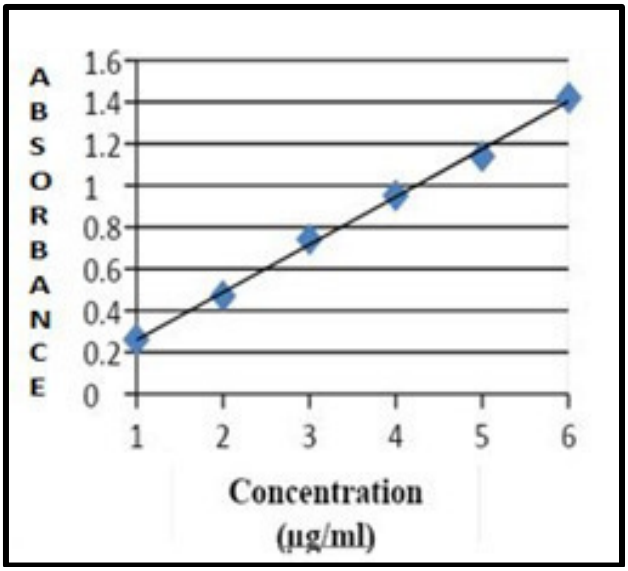

Fig No.2: Calibration curve of Pregabalin

4.3 Compatibility studies

FTIR spectrum of pure Pregabalin, Pregabalin and polymers, Pregabalin and PEG 400, Pregabalin filaments and tablets are shown in figure 3a, 3b, 3c, and 3d.The compatibility between Pregabalin and polymers was evaluated using the FTIR peaks matching method. There was no appearance or disappearance of peaks in the Drug and excipients mixture, which confirmed the absence of any chemical interaction between the drug and excipients.

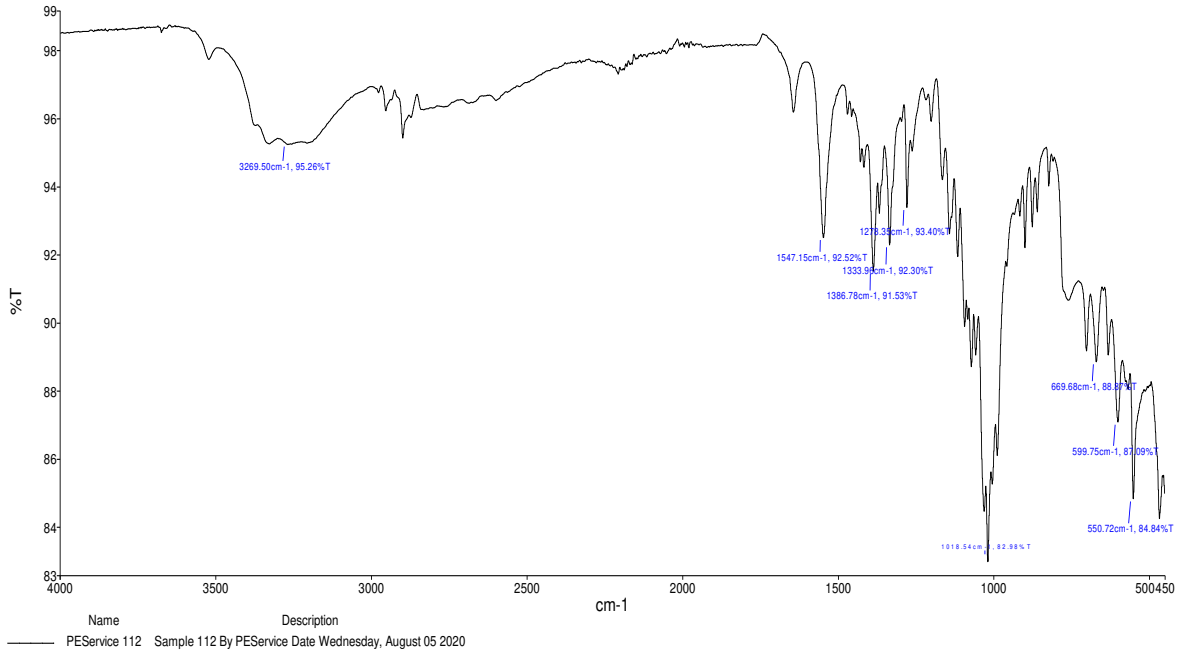

Fig No. 3a: FTIR spectrum of Pure Pregabalin

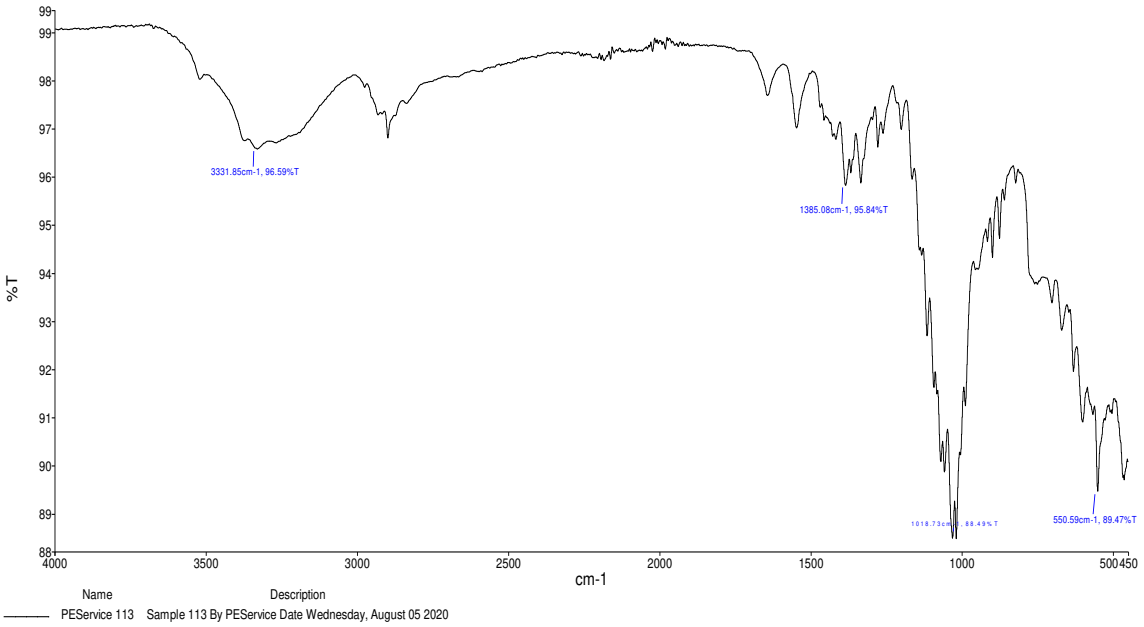

Fig No. 3b: FTIR spectrum ofPregabalin and HPMC E15 LV polymers

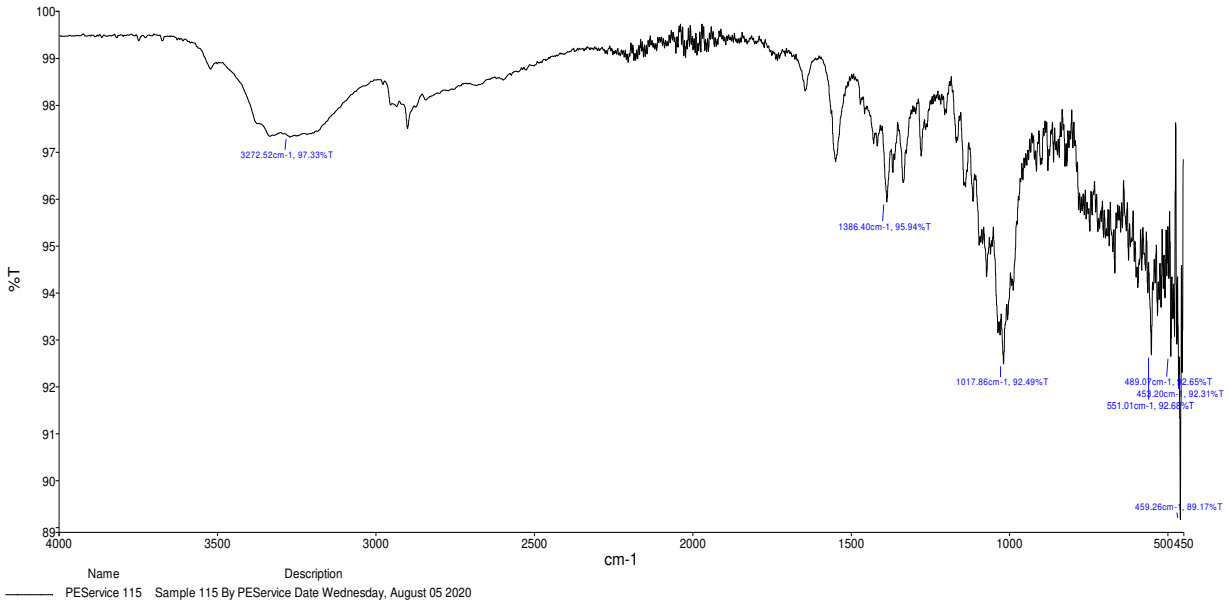

Fig No. 3c: FTIR spectrum of Pregabalin and PEG 400

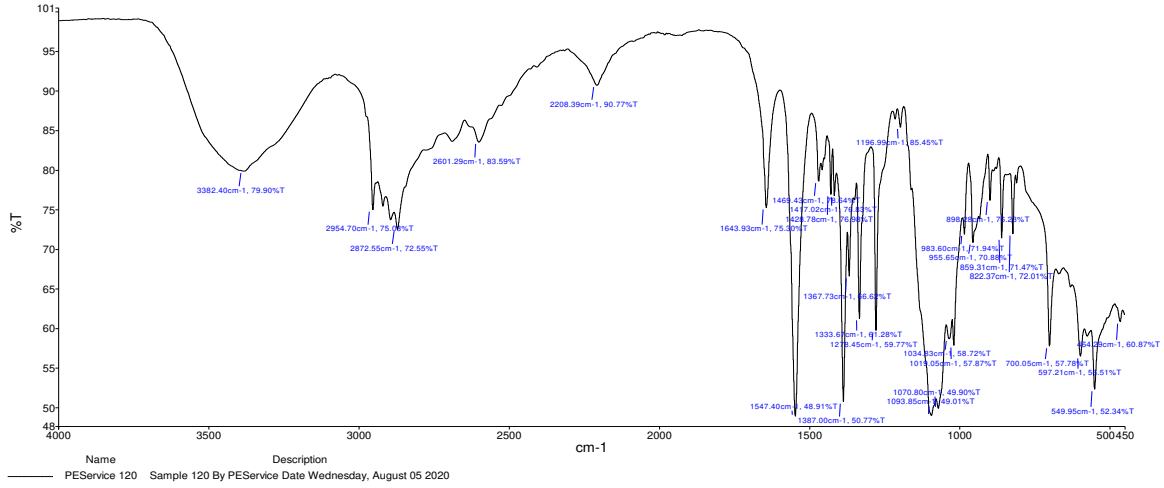

Fig No. 3d: FTIR spectrum of3D printed Pregabalin filament

Pure Pregabalin (figure no. 3a) showed peaks at 3269.50 cm-1 (C–H stretch), 1547.15 cm-1(N–O asymmetric stretch), 1386.78 cm-1 (C–H rock), 1333.96 cm-1 (N–O symmetric stretch),1018.54 cm-1 (O-H Bend) . Pregabalin with HPMC E15LV Polymer (figure no. 3b) shows peaks at 3272.52 cm-1 (C–H stretch), 1386.40cm-1 (C–H rock), 1333.85 cm-1 (N–O symmetric stretch), 1018.73 cm-1 (O-H bend). Pregabalin with PEG 400 (figure no. 3c) shows peak at 3272.52 cm-1 (C-H strech) 1548.15 cm-1(N–O asymmetric stretch), 1386.40 cm-1 (C–H rock), 1335.16 cm-1 (N–O symmetric stretch),1017.86 cm-1 (O-H Bend), 3D Printed Pregabalin filament (figure no. 3d) shows peak at 3382.40 cm-1 (C–H stretch), 1547.40 cm-1(N–O asymmetric stretch), 1367.78 cm-1 (C–H rock), 1333.67 cm-1 (N–O symmetric stretch),1019.05 cm-1 (O-H Bend) As the sharp characteristic peaks of Pregabalin did not change in the formulations with polymer and different excipients, indicating no possible interaction.

4.4 Scanning electron microscopy

SEM imaging shows the surface morphology of Pregabalin filament at various magnifications in fig no. 4. Drug loaded filaments showed irregular surfaces and remained in crystalline form.

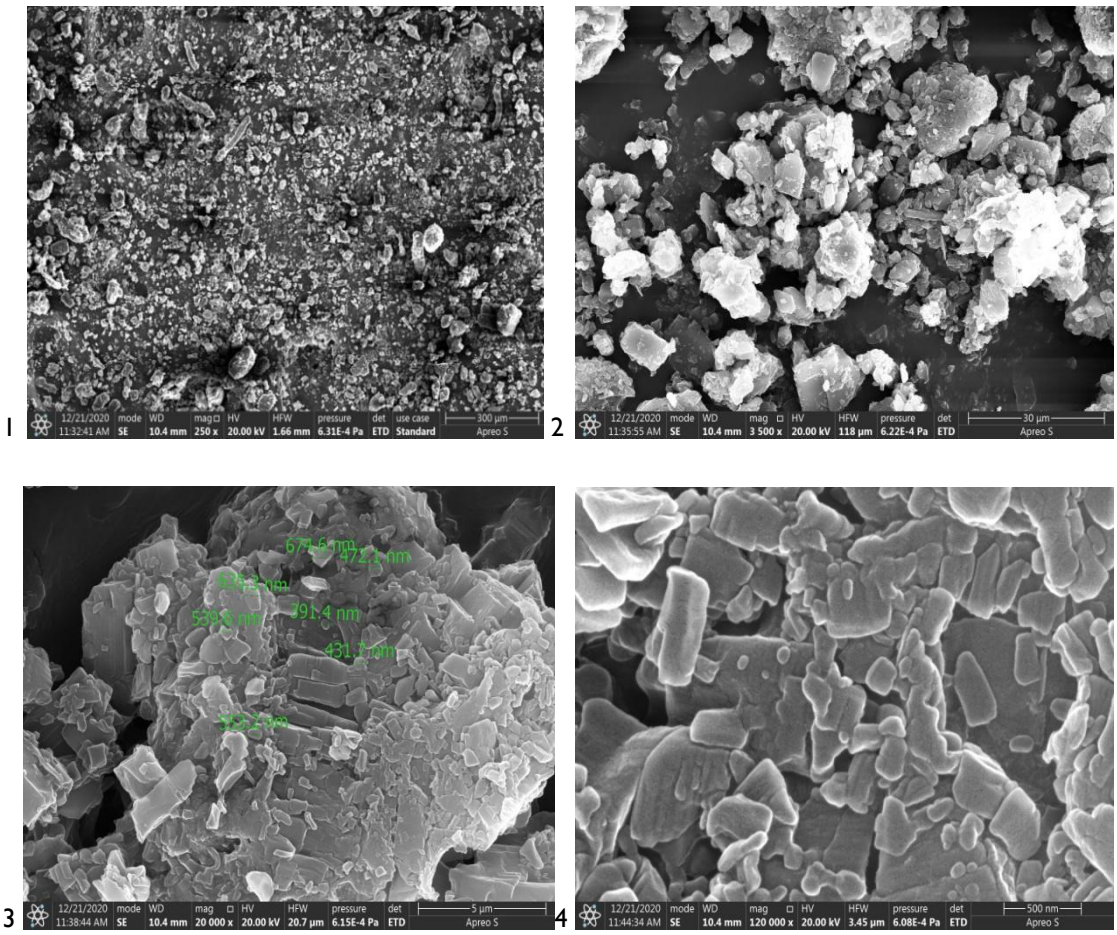

Fig No. 4: Scanning electron microscopy (SEM) image of Pregabalin filament at 1) 250X, 2) 3500X, 3) 20000X and4) 120000X magnifications.

Table No.3- Different formulation of disintegration time

Sr. no	Infill X1 (%)	DimensionX2 (mm)	Print speed X3 (rpm)	Disintegration time (sec)
1	50	15	10	125
2	80	5	15	105
3	25	7.5	10	102
4	25	5	15	109
5	50	5	10	90
6	80	7.5	15	98

Table 3 Showing disintegration time of drug filaments. Each drug filament has a different disintegration time. Changes in variables (infill, dimension, printing speed) affects the disintegration time . From the table, it is clear that infill percentage, dimension of pregabalin filament and print speed affect the disintegration time. The maximum disintegration time is found at infill percentage 50 having dimension of 15mm, and least disintegration time is also found at infill 50 but at dimension 5mm.

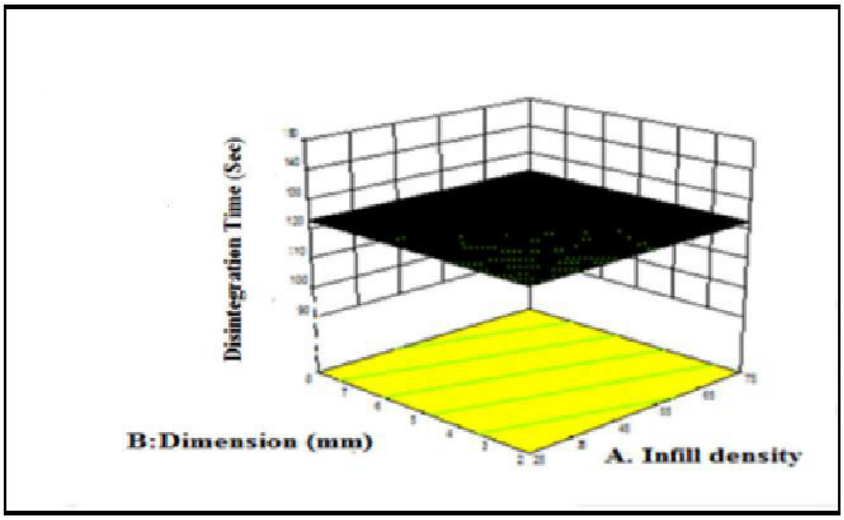

Fig. no. 5: Response surface diagram showing combined effect of infill density and dimensions kept at lower level i.e. printing speed 5rpm.

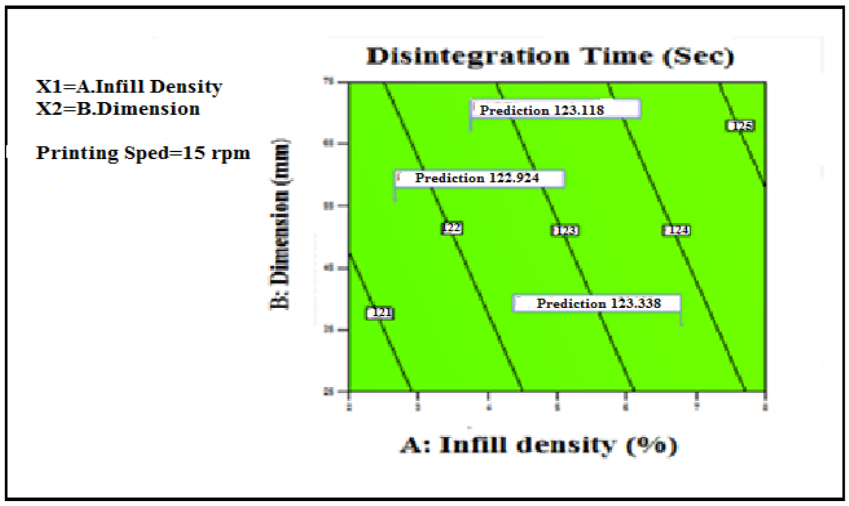

Fig. no. 6: Counter plot showing combined effect of infill density and dimensions kept at lower level i.e. printing speed 5rpm.

Fig No.7: Preparation of Drug Loaded Filament

Table No.4 – Pre-formulation Parameter

Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (^{0})	Carr's index (%)	Hausner's Ratio
F1	0.28±0.0024	0.35±0.0033	32.15±0.26	20.0±0.12	1.25±0.011
F2	0.28±0.0019	0.36±0.0023	34.31±0.31	22.0±0.17	1.28±0.025
F3	0.26±0.00021	0.32±0.0025	34.24±0.31	18.7±0.09	1.23±0.009
F4	0.28±0.0022	0.37±0.0019	28.44±0.22	24.3±0.22	1.32±0.005
F5	0.26±0.0016	0.33±0.0023	31.25±0.12	21.2±0.17	1.26±0.008
F6	0.30±0.0010	0.35±0.0060	33.36±0.30	21.6±0.20	1.27±0.010

Values are mean±SD; (n=3)

Table 4 Showing various pre-formulation parameters like bulk density, tapped density, angle of repose, Carr's Index, Hausner's ratio for each drug filament. F6 has highest and F3 has lowest bulk density. The tapped density of F4 is highest and F3 is lowest. The angle of repose is highest for F2 and is lowest for F4.

F4 has highest and F3 has lowest Carr's Index. Bulk density and tapped density determine the volume occupied by the powder bed. The Hausner's ratio is lowest for F3 and highest for F2.Powder flow properties are determined by determining the angle of repose, Carr's index, and Hausner's ratio.

Table No.5 – Evaluation parameters of 3D Printing Pregabalin Tablets

Formulation	Dimension (mm)	Infill (%)	Shell thickness(mm)	Weight (mg)	Density (g/cm^3)	Drug content (mg)	Drug Loading (%)
F1	12×8	25	0.6±0.231	148.21±0.12	0.40±0.0003	168.22±3.71	93.08±1.54
F2	12×8	50	0.6±0.241	147.29±0.32	0.52±0.0091	227.75±3.53	96.80±1.26
F3	12×8	75	0.6±0.262	149.34±0.11	0.74±0.0304	322.75±10.25	96.80±3.22
F4	12×8	25	0.4±0.301	148.12±0.23	0.55±0.0050	235.95±7.70	94.64±3.03
F5	12×8	50	0.4±0.232	148.42±0.33	0.76±0.0156	335.47±7.10	97.08±2.06
F6	12×8	25	0.4±0.235	149.92±2.57	0.75±0.0145	234.90±12.97	98.52±5.40

Values are mean±SD ;(n=3)

Table 5 Shows different evaluation parameters for 3D printing of Pregabalin Tablets. It includes dimension of tablet, infill, the thickness of shell, weight of tablet, density of tablet, drug content in the tablet, and drug loading. The dimensions of all the formulation is same (12x8 mm). The infill percentage determine the inside part occupied by the material. F3 has highest infill percentage. The shell thickness of all the formulations varies in between 0.4 to 0.6 mm. The weight of the formulations is nearly equal and ranges from 148 -150 mg. The density of F5 is highest and F1 is lowest. The drug content in F3 and F4 is high while in F1 is very low if compared with other formulations.

Table No. 6- Invitro drug release

Time (Hrs)	% Drug release					
	F1	F2	F3	F4	F5	F6
2	79.99	80.13	80.22	80.36	67.31	67.87
4	81.72	81.19	81.72	85.82	70.90	77.29
8	87.86	87.57	87.86	89.64	81.16	81.39
12	90.96	90.58	90.96	91.70	88.80	92.11
24	92.01	94.21	99.44	99.48	99.48	99.62

Table 6 Shows invitro drug release in percentage of different drug filaments at different intervals of time. In 2 hours , F5 has lowest drug release and F4 has highest drug release. In 4 hours, F4 has highest drug release and F5 has lowest drug release. After 8 hours, F4 has highest drug release and F5 has lowest drug release. F4 and F5 follows the same pattern for 2, 4, and 8 hours. After 12 hours , F6 has highest drug release and F5 shows lowest drug release. After 24 hours F6 still shows highest drug release while F1 shows lowest drug release.

Invitro release profile of 3D printing Pregabalin Tablets

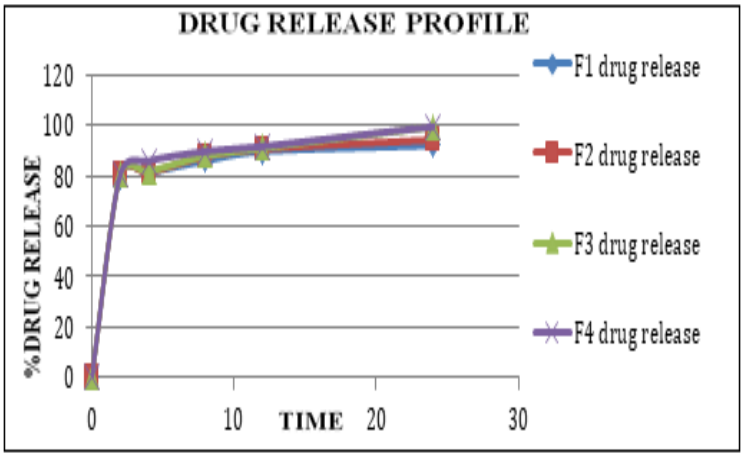

Fig No. 8: Invitro dissolution profile of 3D printing Pregabalin tabletsF1 to F4.

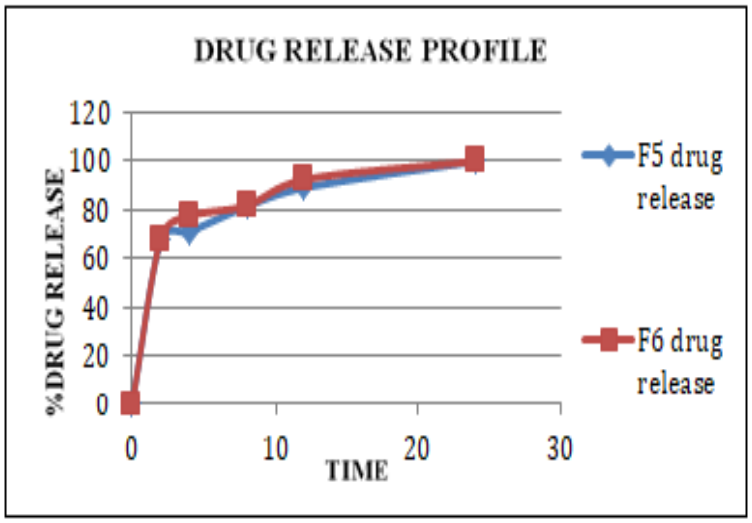

Fig No.9: Invitro dissolution profile of 3D Printing Pregabalin tablets F5 and F6.

4.5 Kinetic analysis of dissolution data

The invitro data is fitted into different kinetic models and the best-fit was achieved with the Pappas model.

Table No. 7-Kinetic analysis for different formulations

Formulation	Zero Order (R)	First Order (R)	Matrix (R)	Hix-Crow (R)	Peppas		Best Model Fit
					(R)	(N)	
F1	0.9981	0.9984	0.9659	0.9956	0.9990	0.6572	ZERO
F2	0.9982	0.9503	0.9579	0.9784	0.9888	0.8858	PEPPAS
F3	0.9985	0.9921	0.9613	0.9978	0.9999	0.9181	PEPPAS
F4	0.9922	0.9904	0.9692	0.9945	0.9892	0.7570	HIXCROW
F5	0.9984	0.9425	0.9609	0.9771	0.9989	0.8815	PEPPAS
F6	0.9993	0.9846	0.9661	0.9956	1.0000	0.9373	PEPPAS

Table 7 Showing results of kinetic analysis of different formulations and it also shows the best model fit for each formulation. Based on the correlation coefficient (r) value in various models, the best fit model was selected. When the invitro data is fitted into different kinetic models the best-fit was achieved with the Pappas model. Out of all the formulations F6 shows the best Correlation coefficient for zero order, Hix-crow and Peppas. The N value 0.9373 was also best for formulation F6 among all the formulated formulation from F1-F6.

4.6 Stability Studies

The stability study was conducted by following the ICH guidelines. It showed no significant change in properties of the optimized formulation and drug release. Stability studies were performed in a stability chamber over a period of 3 month on the promising 3D Printed Pregabalin tablets formulation F6. Sufficient number of tablet formulations were packed in a stability container and kept in a stability chamber at Temperature 45°C and RH 75%. Samples were taken for 90 days for drug content estimation; also the appearance, weight, dimension, shell thickness and invitro dissolution studies were performed to determine the drug release profile. The detailed invitro % drug release stability data were shown in the stability parameter (Evaluation) of 3D printed Pregabalin tablets shown in Table no-8.

Table No.8 Stability parameter (Evaluation) of 3D printed Pregabalin tablets

Parameter	Initial	After stability
Shape	Round	Round (no change)
Colour	Yellow	Yellow (no change)
Dimension (mm)	12×8	12×8
Shell thickness (mm)	0.4	0.4
Weight (mg)	149.92±2.57	149.92±2.57

Table 8, Shows invitro % drug release stability data of 3D printed Pregabalin tablet. Stability studies were performed in a stability chamber over a period of 3 month on the promising 3D Printed Pregabalin tablets formulation F6. Sufficient number of tablet formulations were packed in a stability container and kept in a stability chamber at Temperature 45°C and RH 75%. Samples were taken for 90 days for drug content estimation; also the appearance, weight, dimension, shell thickness and invitro dissolution studies were performed to determine the drug release profile.

5. DISCUSSION

In the present study an attempt has been made to formulate and evaluate 3D printed Pregabalin tablets for the treatment of neuropathic pain by QbD approach. Pre formulation studies were performed to evaluate the different properties of the Pregabalin and found satisfactory. The study reveals that all the parameters for sustained release were acceptable. The Fourier transform infra-red analysis was conducted for the surface structure characterization. FTIR spectrum of the formulated sustained release tablets, pure drug and excipients was recorded. It was similar to peaks found in previous study.[25]The 3D Printed tablet formulation of Pregabalin was done by using the QbD approach. In the QbDapproach, disintegration time was used in the formulation. Croscarmellose sodium was used as a disintegrating agent. The disintegration time of all formulations was checked by using Software 9.0.5 Central Design Expert. The effect of these factors on the physical characteristic of the formulated 3D Printed tablet was examined i.e. infill 50 %, dimension 5mm & the print speed was obtained 10 rpm. The result of disintegration time (Sec) is shown the measured values from the experimental trials revealed wide range (90-125 Sec) disintegration time while in the previous study development of age-appropriate pediatric formulation of baclofen minicaplets, 3 level-2 factor (32) full factorial design was used as a DoE tool by multiple regression analysis, effect of independent variables, i.e. dimensions(X) and infill pattern were studied on drug release i.e. approximately 75% of drug release occurs at 1hr.[26] The SEM image of drug loaded Pregabalin filaments showed irregular surface and remained in crystalline form as compare to SEM image of Dipyridamole or theophylline loaded filaments 3D printing immediate release tablets were produced via processing a physical mixture of API (10%) and PVA in the presence of plasticizer through hot-melt extrusion (HME) showed that the structure of filament was smooth with few apparent gaps or voids and the SEM image age-appropriate pediatric formulation of baclofen minicaplets,[3] shows homogeneous surfaces without any abrasions were observed suggesting the formation of a homogenous system after extrusion processing.[26] The tablets were formulated by fused deposition modeling manufacturing process. All formulations were checked for shape, colour, weight variation test, friability, invitro dissolution studies, accelerated stability study and results were within the limits. Standard calibration curve of Pregabalin obeys the Beer's law in the range between 2-12µg/ml. Bulk density (0.25±0.0021 to 0.30±0.0010 gm/cm3) and Tapped density (0.31±0.0025 to 0.37±0.0019 gm/cm3) values are within the limits. The values obtained for angle of repose for all formulations are tabulated in table the values were found to be in the range from 28.44±0.21-34.31±0.32. Carr's index (18.7±0.08 to 24.3±0.23) and Hausner's ratio (1.23±0.008 to 1.32±0.006) values are within the limits, indicating that the Pregabalin having the required flow property and % Drug release determined by Invitro dissolution studies (Table 6). The in-vitro dissolution studies were carried out by using USP type-II apparatus in a 6.8 pH phosphate buffer. Among all the formulations (F1 to F6) prepared, batch F6 is the best formulation released 99.62 % at the end of 24 hours. In a previous study, formulation prepared with HPMCAS HG was not completely dissolved even after 24 hours and drug release was pH- sensitive as the enteric polymer was distributed into the matrix rather than as a coating layer in conventional formulations. From the above result it is concluded that formulated 3D printed Pregabalin tablets show significant effect in the treatment of neuropathic pain.

6. CONCLUSION

In the pharmaceutical sector, 3D printing has become an essential and potential tool, leading to personalized medicine focused on the patients needs. In this study, drug loaded feedstock material for FDM 3D printing was prepared utilizing hot - melt extrusion. All printable formulations showed good correlation between the printed tablets size as well as weight of the tablets, focusing the potential to use 3D printing for production of personalized doses for treatment of neuropathic pain. Quality by design, is an essential part of the modern approach to pharmaceutical quality. Identification of critical material attributes that provide a link to the product quality to the manufacturing process. In the QbD approach, disintegration time is used for the formulation. All 6 formulations were checked forthe disintegration time by using software of a central design expert. Different Formulations of 3D printing tablets were observed, where F6 formulation was found to be the best formulation, and had sustained release of 3D printed Pregabalin tablets over 24 hour and was considered as the good release i.e. (99.62%). From the above result, it was concluded that prepared 3D printed Pregabalin tablets have been found to have good potential for prolonged drug release and hence it can be beneficial for use in the treatment of neuropathic pain.

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8. AUTHORS CONTRIBUTION STATEMENT

Mule Shrikrishna gathered data, perceived the idea, carried out the research study with regard to this work. Dr Om prakash guided conducted this research study and reviewed the manuscript. Dr. Gaurav Agarwal analyzed the data and gave necessary inputs towards the designing of the manuscript. All authors provided critical feedback, discussed the methodology, results and contributed to the final manuscript. All the authors read and approved the final version of the manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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